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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/098,502	03/18/2002	Rohini Ramesh Joshi	033432-017	4414

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EXAMINER	
COPPINS, JANET L	
ART UNIT	**PAPER NUMBER**
1625	

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/098,502	JOSHI ET AL.	
	Examiner	Art Unit	
	Janet Coppins	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-6 pending in the instant application.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-6 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated in the MPEP 2164.01(a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case, claims 1-6 recite a process for the preparation of [S(-) amlodipine-L(+)hemi tartarte].

The nature of the invention

The nature of the invention is of a process for the preparation of [S(-) amlodipine-L(+)hemi tartarte] in good yield and high enantiomeric purity by reacting RS amlopdipine base with L(+) tartaric acid in an organic solvent, to obtain S(-)-amlodipine.

The state of the prior art

It is the state of the prior art that chiral compounds can be synthesized in the form of a single enantiomer, rather than as a mixture of stereoisomers, and that this process can be done via asymmetric synthesis, or stereoselective synthesis. The state of the art teaches that a pair of enantiomers (i.e. RS amlodipine base) can be separated by utilizing an active reagent, catalyst, or solvent (i.e. L(+)-tartaric acid) that reacts faster with one of them than it does with the other (i.e. resolution). (*Advanced Organic Chemistry*, pages 116-119). The prior art teaches that reacting the RS mixture of amlodipine with L-tartaric acid in DMSO will precipitate R(+)-amlodipine and reacting with D-tartaric acid in DMSO will precipitate S(-)-amlodipine.

The predictability or lack thereof

The predictability or lack thereof in the art is that if the absolute configuration of the reagent is known, the configuration of the enantiomers can often be determined by a knowledge of the mechanism and by seeing which diastereomers is preferentially formed. Furthermore, since racemic acid is actually a mixture of (+) and (-)- tartaric acids, the racemic solution can be seeded with something that will cause only one enantiomer to crystallize; i.e. all the (+) molecules going into one crystal and all the (-) into another. Therefore one skilled in the art would be able to predict which enantiomer would form in this enantioselective reduction method

based upon the specific enantiomer of chiral reagent that is utilized. (*Advanced Organic Chemistry*, pages 120-124).

The amount of direction or guidance present and the presence or absence of working examples

The only direction or guidance present in the specification and the only working examples present in the specification are for the preparation of amlodipine hemi L tartarate-mono-DMSO solvate, R(+)amlodipine-hemi-L-tartarate mono DMSO solvate and S(-) amlodipine-hemi-L tartarate mono DMSO solvate, starting from (RS) amlodipine, of Example 1 (the remaining Examples do not disclose the entire preparation from (RS) amlodipine).

The breadth of the claims

The breadth of claims 1-6 is a process for the preparation of [S(-) amlodipine-L(+)hemi tartarte] in good yield and high enantiomeric purity by reacting RS amlopdipine base with L(+) tartaric acid in an organic solvent, filtering out [R(+)amlodipine-L(+)-hemi tartarte], seeding the filtrate to obtain [S(-) amlodipine-L(+)hemi tartarte], then filtering, recrystallizing, and basifying to obtain S(-) amlodipine.

The quantity of experimentation needed

The quantity of experimentation is extremely high. Since the prior art teaches away from the instantly claimed procedure, one would need to practice the invention numerous times in order to accept the procedure.

The level of skill in the art

The level of skill in the stereochemical art is high. However, without further guidance as to how to make the S(-)-amlodipine enantiomer from the RS-amlodipine base with L(+) tartaric

acid, particularly when the prior art teaches away from this process, it would require undue experimentation to determine what active reagents, solvents, temperatures and reaction times would provide the desired enantiomer from the alleged enantioselective reduction.

Since the claimed invention is not supported by either a credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 1-6 rejected under 35 U.S.C. 101 because the disclosed invention is inoperative and therefore lacks utility. Please refer to MPEP 2107.01:

> An invention that is "inoperative" (i.e., it does not operate to produce the results claimed by the patent applicant) is not a "useful" invention in the meaning of the patent law. See, e.g., Newman v. Quigg, 877 F.2d 1575, 1581, 11 USPQ2d 1340, 1345 (Fed. Cir. 1989); In re Harwood, 390 F.2d 985, 989, 156 USPQ 673, 676 (CCPA 1968) ("An inoperative invention, of course, does not satisfy the requirement of 35 U.S.C. 101 that an invention be useful.")

As stated above, in the description of asymmetric synthesis: if the absolute configuration of the reagent is known, the configuration of the enantiomers can often be determined by a knowledge of the mechanism and by seeing which diastereomers is preferentially formed. Furthermore, since racemic acid is actually a mixture of (+) and (-)- tartaric acids, the racemic solution can be seeded with something that will cause only one enantiomer to crystallize; i.e. all the (+) molecules going into one crystal and all the (-) into another. Therefore one skilled in the art would be able to predict which enantiomer would form in this enantioselective reduction method

based upon the specific enantiomer of chiral reagent that is utilized. (*Advanced Organic Chemistry*, pages 120-124). It would be obvious to one skilled in the art that by using the L(+) form of tartaric acid, then the R(+) form of amlodipine base would be obtained, as evidenced in the prior art (U.S. Pat. No.'s 5,750,707; 6,057,344; 6,046 338; WO 03/035623; EP 1181932, for example). Since the prior art, in fact, teaches away from the results of the instantly claimed invention, i.e. the claimed results would not be possible, and therefore the process is wholly inoperative.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet Coppins whose telephone number is 703.308.4422. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Alan Rotman can be reached on 703.308.4698. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Janet L. Coppins
March 5, 2004

Joseph McKane,
Acting SPE, Art Unit 1625